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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/581,528	10/26/2000	Masatoshi Takeda	P19743	6685

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,528	TAKEDA ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *3,4,10,11,18-32,34,35 and 43-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-9,12-17,33 and 36-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8, 23* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of the invention of claims 1, 2, 5-9, 12-17, 33, 36-42 (group I) in Paper No. 22 is acknowledged. The traversal is on the ground(s) that the restriction requirement fails to set forth a prima facie case for a serious burden. This is not found persuasive because applicants have ignored the directive for restriction in MPEP 803. Applicants' attention is drawn to the first sentence of MPEP 803, which states,

"Under the statute an application may properly be required to be restricted to one of two or more claimed inventions only if they are able to support separate pat-ents and they are either independent (MPEP § 806.04 - § 806.04(i)) or distinct (MPEP § 806.05 - §806.05(i))." It is noted that the restriction requirement set forth in the previous office action was in accordance with MPEP 803." It is noted that the restriction is not only for serious search burden but also if the inventions are distinct and in the instant case that is the case. Additionally, search burden is another factor in the instant case because searching for mutation at one amino acid will not be coextensive with another mutation. Likewise, search for a particular plasmid with certain sequence will not be coextensive with the search for another plasmid with another sequence. Applicants have not provided any evidence to indicate that the inventions are not distinct.

Regarding applicants' arguments that unity of invention of claims should be followed in international applications, it is noted that such a practice was followed. The basis for lack of unity was that the inventions of the groups lack a special technical feature. In the instant case, the mutant presenilin-1 mutants have mutations at different amino acids and that there are different mutations of presenilin-1 gene in Alzheimer disease families. And the lack of unity was set forth according to PCT Rules CFR 37 174.5 (d), which states,

"If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be

considered as the main invention in the claims, see PCT Article 17(3)(a) and § 1.476(c)."

In response to applicants' arguments that the examiner has not defined as to "what is materially different", it is noted that applicants seem to have ignored the explanation given in the restriction requirement. Applicant's attention is drawn to the restriction requirement of 7-22-02, part of which is reproduced below:
"The invention of group I lacks the same technical feature as those of the groups II-V and XVI because they comprise different transgenes with different mutations in the transgene. Additionally, the characteristics of the animals of one group would be different from those of the other group. It is noted that a mutant presenilin-1 gene could comprise any mutant, however, one mutant would lack the same technical feature as the other one because two different mutations may affect a protein function differently. It is well known in the prior art that alteration of one single amino acid would alter the function of a protein. "

Applicants' arguments that the applicant has paid a filing fee for en examination of all claims is not relevant because there is no provision in the MPEP that filing of fee should guide what is examined in the application.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 3, 4, 10, 11, 18-32, 34-35 and 43-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 22.

3. Claims 1, 2, 5-9, 12-17, 33 and 36-42 are under consideration.

Claim Rejections - 35 USC § 112

4. Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instantly claimed invention encompasses any non-human animal that is gene mutated and has a mutant presenilin-1 gene and method of using the animal. transgenic

The specification provides example of making a knockout transgenic mouse whose Presinilin-1 gene has a mutation of isoleucine at 213 has been mutated. The specification also teaches plasmid to make the transgenic mouse. In analyzing whether the written description requirement is met, it is first determined whether the whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences of altering the genotype have been described. In the instant case, the claimed invention encompasses knockout animals, non-transgenic animals in which the expression of the recited gene is either inhibited or activated, or transgenic animals in which exogenous transgene expressing the recited gene has been introduced. Considering the fact that the claimed invention encompass transgenic animals as well as knockout animals or non transgenic animals, and there is no description of the phenotype of any animal, the phenotype(s) of the claimed animals can not be predicted because the art of making transgenic animals or knockout animals is highly unpredictable. The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

This clearly indicates that the phenotype of a transgenic mouse or rat or any animal cannot be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genus.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In case of a knockout animal, it is not possible to adequately describe the claimed animals because the effects of inactivating a gene cannot be predicted, particularly when a gene product may be interacting with the proteins of a family of proteins. For example, Korach et al (US Patent No. 5,650550) produced a knockout mice lacking a functional estrogen receptor. One skilled in the art would not have predicted that such an animal would even be viable (see col 9, lines 22-39), much less have been able to predict the resulting phenotype. In the instant application, what would have been the result of the mutating presenilin gene at any amino acid cannot be predicted in the transgenic animals encompassed by the invention. With the limited information disclosed in the specification, an artisan would have not been able to predict whether all these animals would have had same or different phenotypes compared to the knockout mice or transgenic mice.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a knockout transgenic mouse whose endogenous presenilin-1 gene has been mutated by

homologous recombination, a cell isolated from the transgenic mouse and a method of using the transgenic mouse for evaluating therapeutic compound that is useful in treating or preventing Alzheimer's disease, does not reasonably provide enablement for any other embodiments of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

At the time of the instant invention, the art of transgenic animal research had several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter

sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. In an assessment of the transgenic technology at the time of the invention, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

For example, Hammer et al (Hammer RE et al. Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address this issue?

Introduction of foreign DNA into fertilized oocyte , for example by micro injection, may result in random integration of the exogenous DNA into host

chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will express the transgene to a level high enough so as to enable the development of the claimed phenotype in the transgenic animals.

The art of culturing and maintaining ES cells in culture is unpredictable. Gardner and Brook (Gardner RL and Brook FA. International J. of Dev. Biol. 41:235-243, 1997) summarized the progress in the field of ES cell biology, "Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most stains have so far proved refractory to the derivation of cell lines....." Additionally, gene targeting and selection of the ES cells that harbor the integration of a desired construct also has been shown to be unpredictable in animals other than mice. To prevent their differentiation, ES cells are maintained in culture in the presence of mouse derived factors that inhibit differentiation either by coculturing the cells in the presence of feeder cell lines or by adding agents to the culture as a media supplement. However, it has been suggested that the such differentiation-inhibitory derived from mouse do not adequately prevent differentiation of stem cells in species other than the mouse. For example, rat ES cells, capable of producing chimeras, grow best on primary rat embryonic fibroblasts as the feeder layer (see last para in col 1 on page 1558 in Mullins and Mullins, 1996) (Mullins LJ and Mullins JJ. J. Clin. Invest.97:1557-1560, 1996).

The art of transgenesis based on ES cells is unpredictable.The art of transgenesis based on ES cells is unpredictable. Seamark (Seamark, Reprod. Fertil. Dev. 6: 653-657, 1994) states that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract on page 653). He further adds that although various studies have provided insight into what this new

technology could offer to the livestock breeder, scientific and technical challenge still confront the molecular and reproductive biologist attempting to make the technology available to serve this purpose (page 653, 3rd paragraph).

The steps of producing a knockout animal include, isolating the gene, destroying the gene by inserting therein a selectable marker gene, introducing vectors incorporated with the destroyed gene into cultured ES cells thereby allowing homologous recombination to occur, isolating and identifying a clone in which homologous recombination has been effected, injecting the clone into a blastocyst that develops into the desired mouse. While the steps to produce knock out mouse have been well developed and used in mice, they have not been fully developed in other animals, particularly the art of gene targeting in ES cells and culture and selection of the ES cells that harbor the desired integration has been shown to be unpredictable in animals other than mice (as discussed above). Mullins and Mullins (1996) stated "However, at the present time the reliable generation of bovine ES cell lines requires the pooling of inner cell mass from several blastocysts and further efforts are required to enable the long term culture of clonal bovine ES cells. Although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has the germline transmission of an ES cell has been successfully demonstrated " (Page 1558, para 1 in col 2).

The specification does not provide any guidance as to how any other animal in which presenilin-1 gene was mutated would have been produced or how would an artisan cultured ES cells of any other animal than of mouse, target presenilin-1 gene in the ES cells and produce a transgenic animal. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Therefore, the specification fails to provide any guidance as to how an artisan would have dealt with the art recognized limitations of the method for making any and all transgenic animals and therefore, the creation of any and all non-mouse animals would have necessitated undue experimentation on the part of an artisan. Accordingly, limiting the scope of claimed invention to a knockout transgenic mouse

whose endogenous presenilin-1 gene has been mutated by homologous recombination, a cell isolated from the transgenic mouse and a method of using the transgenic mouse for evaluating therapeutic compound that is useful in treating or preventing Alzheimer's disease is proper.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2, 5-9, 12-17, 33 and 36-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite and vague because the claim recites " a non-human gene-mutated animal having a mutant presenelin-1 gene". The metes and bounds of the claimed invention is not clear since it is unclear as to whether the claimed animal has one mutant gene or more than one genes mutated.

Claims 5-9 are indefinite because it is unclear whether sequences set forth in SEQ ID NO 2 or 4 and in SEQ ID NO 1 and 3 disclose the wild type sequence or the mutant sequence.

Claim 12 recites the limitation " amyloid beta protein " in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any such term.

Claim 12 recites the limitation "the mutant presenelin-2 gene" in line 3. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any such term.

Claim 13recites the limitation "the mutant presenilin protein" in line 3. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any such term.

Claim 13 recites the limitation "the mammal" in line 5. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any such term.

Claim 16 recites the limitation "the mutant presenelin-2 gene" in line 3. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any such term.

Claim 17 recites the limitation " amyloid beta expression" in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite any such term.

Claim 36 is vague and indefinite because it is unclear as to what are the steps of the method. It is noted that the claim as instantly presented recites a step of subjecting to comparison and it is not clear what is meant by this step.

Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. It is noted that the only step recited in the method is an administration of a test substance to a gene-mutated animal and subjecting it to said animal not administered with the test substance. It is not clear as to how just administering a substance and comparing with another animal will evaluate that a substance is useful for therapy or prevention of Alzheimer's disease.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

10. Claims 1, 2, 33, 36-42 rejected under 35 U.S.C. 102(e) as being anticipated by Zheng et al (Pub No. US 2002/0016978, filed 5-14-1998, effective filing date 5-14-1997).

This publications teaches a transgenic mouse in which the endogenous presenilin-1 gene has been in activated and a method of identifying compounds using the transgenic mouse (see for example claims 1 and 20). Regarding the SEQ ID NO recited in claim 2, it is noted that the sequences are for human and murine presenilin-1 genes, therefore, they are encompassed by teachings of the publication. Accordingly the invention of claims 1, 2, 33, and 36-42 is anticipated by Zheng et al.

11. Claims 1, 2, 33, and 36-42 are rejected under 35 U.S.C. 102(e) as being anticipated by George-Hyslop et al (US Patent No 6,395,690, filed 7-29-98, effective filing 4-18-1995).

This patent teaches a transgenic mouse expressing human presenilin-1 gene (see claims 1-4; column 5, lines 14-37). This patent also teaches transgenic C.elegans (see example 16). The patent also teaches to use cells and animals for screening of therapeutics (see columns 45 and 46, particularly lines 63-67 in column 45 continued in lines 1-23 of column 46). Accordingly, the claimed invention is anticipated by George-Hyslop et al.

12. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Duff et al (Nature 383:710-713, 1996).

Duff et al teach a transgenic mouse expresses a mutant presenilin-1 (see the entire article). Accordingly, the claimed invention is anticipated by Duff et al.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 5-7, 12-17, 22 and 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamino et al (Neuroscience Letters 208:195-198, 1996) in view of Duff et al (Nature 383:710-713, 1996) or George-Hyslop et al (US Patent No 6,395,690, filed 7-29-98, effective filing 4-18-1995).

Kamino et al teaches mutations in presenilin-1 gene that are present in early onset Alzheimer's disease families. These mutants, listed in table 1, are Val96Phe, His163Arg, and Ile213Thr. Kamino et al does not teach a transgenic mouse that expresses a mutant presinilin 1.

Duff et al teach a transgenic mouse expresses a mutant presenilin-1 (see the entire article). This art also the relationship that in the mutant presenilin 1 transgenic mice expression of beta amyloid is increased in brain of the transgenic mice and that this is correlates with the pathogenic route followed in Alzheimer's disease (see the first paragraph in the left column on page 712). The art also teaches method of making transgenic animals (see page 712-713).

The patent of George-Hyslop et al teaches a transgenic mouse expressing human presenilin-1 gene (see claims 1-4; column 5, lines 14-37). This patent also teaches transgenic C.elegans (see example 16). The patent also teaches to use cells and animals for screening of therapeutics (see columns 45 and 46, particularly lines 63-67 in column 45 continued in lines 1-23 of column 46).

At the time of the invention, it would have been obvious to an artisan to modify the vectors of Duff et al or George-Hyslop et al by mutating the Isoleucine 213 in the murine or human presenilin 1 gene and produce a transgenic mouse with a reasonable expectation of success and use the mouse in methods of evaluating therapeutic or preventive compounds usable in Alzheimer's disease treatment. An artisan would have been motivated to make such a mouse because the mouse would have confirmed the relationship of presenilin 1 gene mutation at Isoleucine 213 as suggested by the studies of Kamino et al and such a mouse could be used for identifying compounds of therapeutic value.

15. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.